Novel approaches for prevention of RSV infection: New anti-RSV monoclonal antibodies

Octavio Ramilo

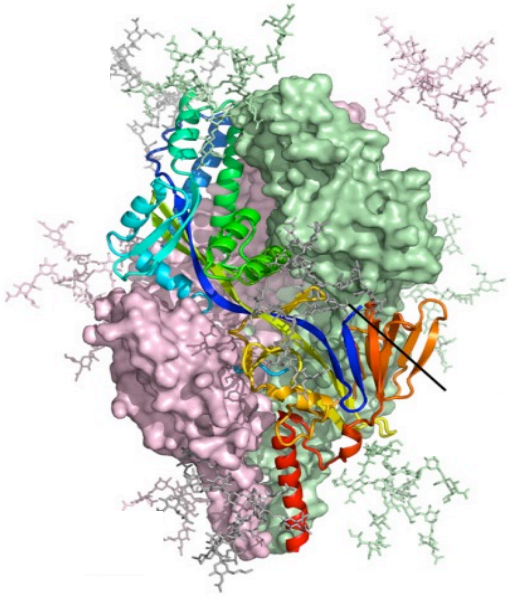
Nationwide Children's
When your child needs a hospital, everything matters.℠

The Ohio State University
College of Medicine

Speaker Disclosure

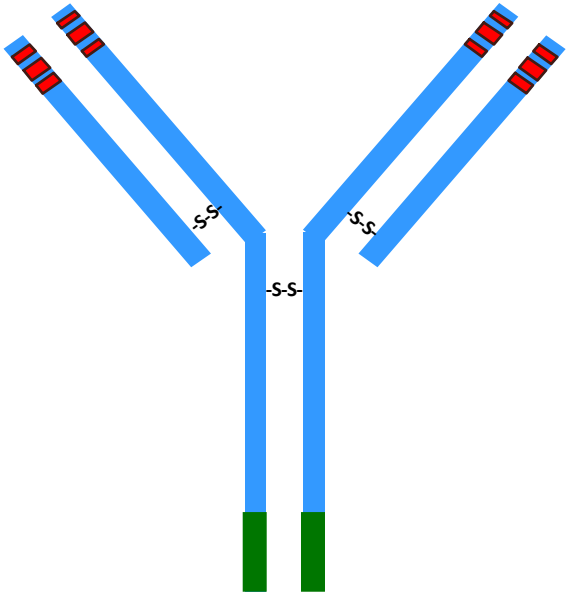
	No, nothing to disclose
x	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Merck		x						
Sanofi/Medimmune		x						
Pfizer	x	x						
NIH: NIAID, NICHD			x					
Janssen			x					
Bill & Melinda Gates Foundation			x					
Ohio Children's Hospital Association			x					



Prefusion F
trimer

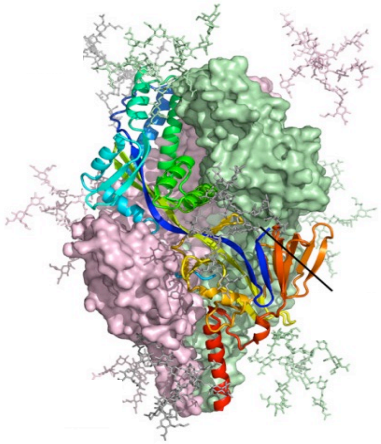
vs



Vaccines

mAbs

Vaccines



Prefusion F
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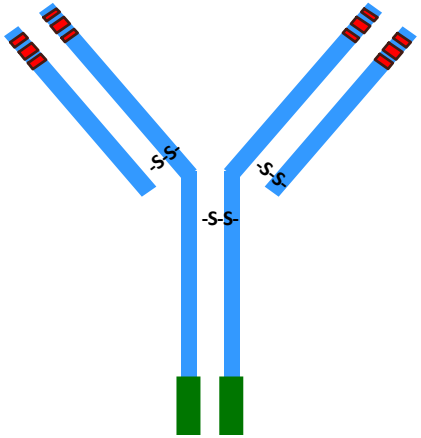
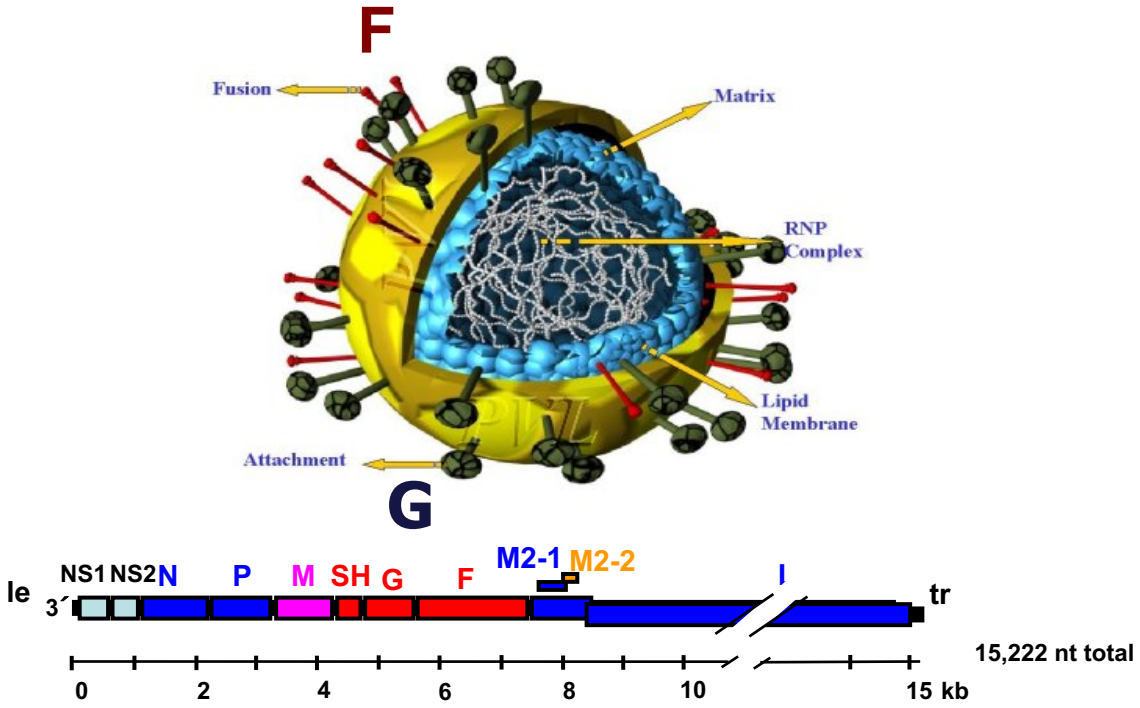


Outline

1. RSV: The virus
2. Rationale for passive immunization for RSV
3. Previous experience with anti-RSV mAbs
4. Structure of Pre- and Post-Fusion F
5. Novel potent neutralizing mAbs with extended half life

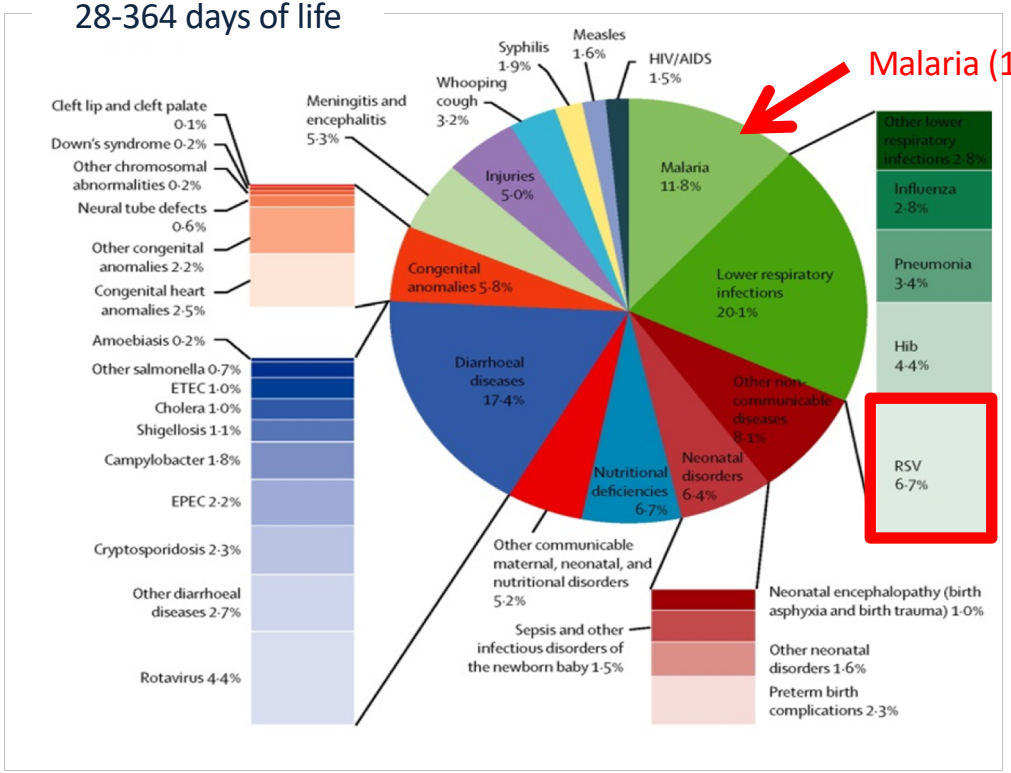
RSV: The Virus

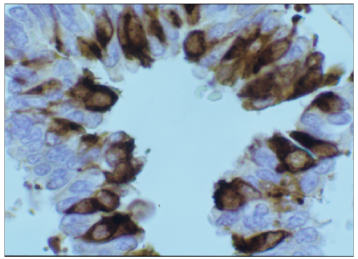


Modified from Park JW, Barnett DW. South Med J 2002; 95:353–7; McLellan JS, Ray WC, Peeples ME. Curr Top Microbiol Immunol 2013; 372:83–104; Collins PL, Fearns R, Graham BS. Curr Top Microbiol Immunol 2013; 372:3–38

Global RSV Disease Burden

RSV kills more children <1 year than any other single pathogen except malaria

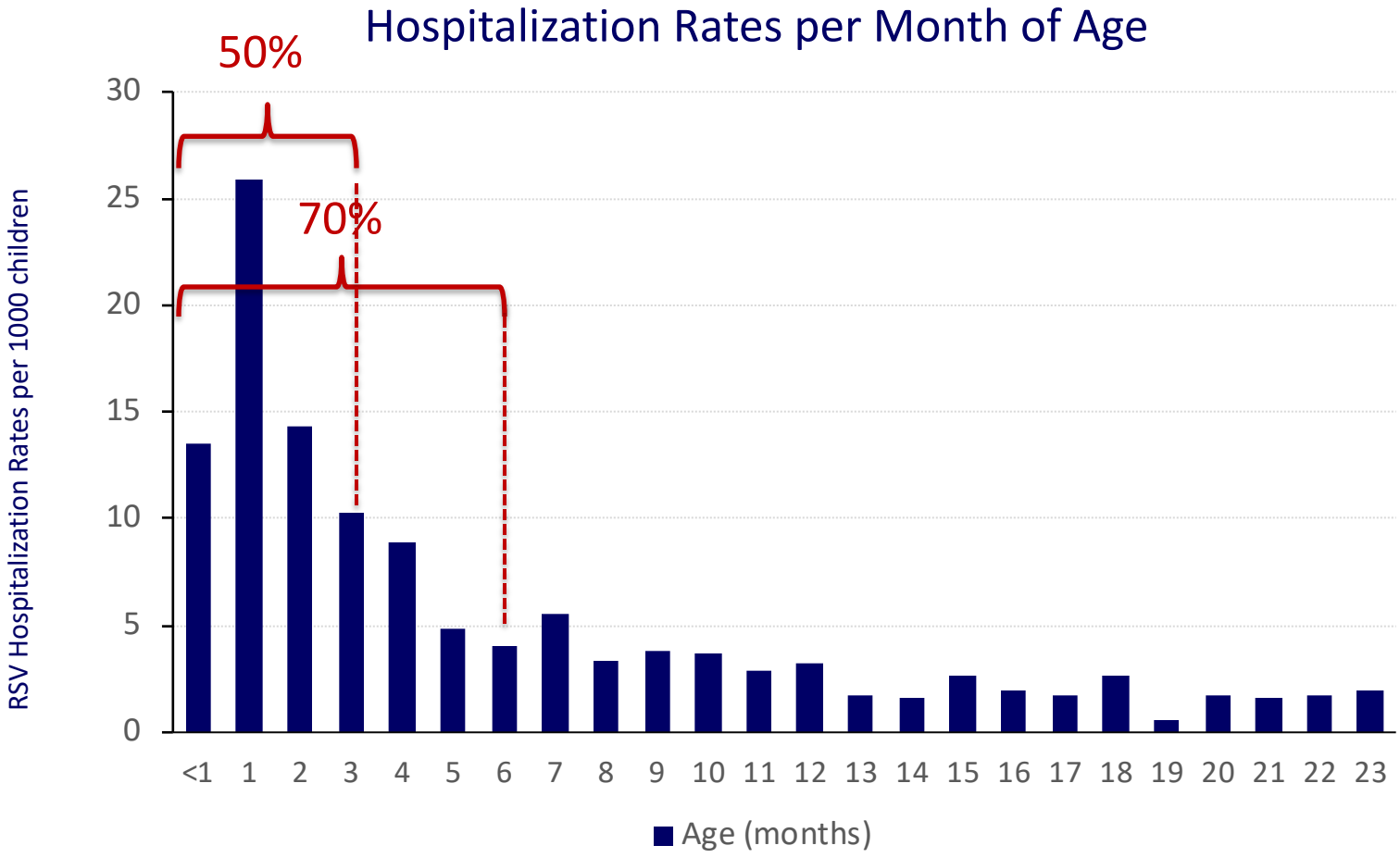




Lozano, R et al. The Lancet. 2012; 380:2095-2128.

RSV: Rationale for passive immunization

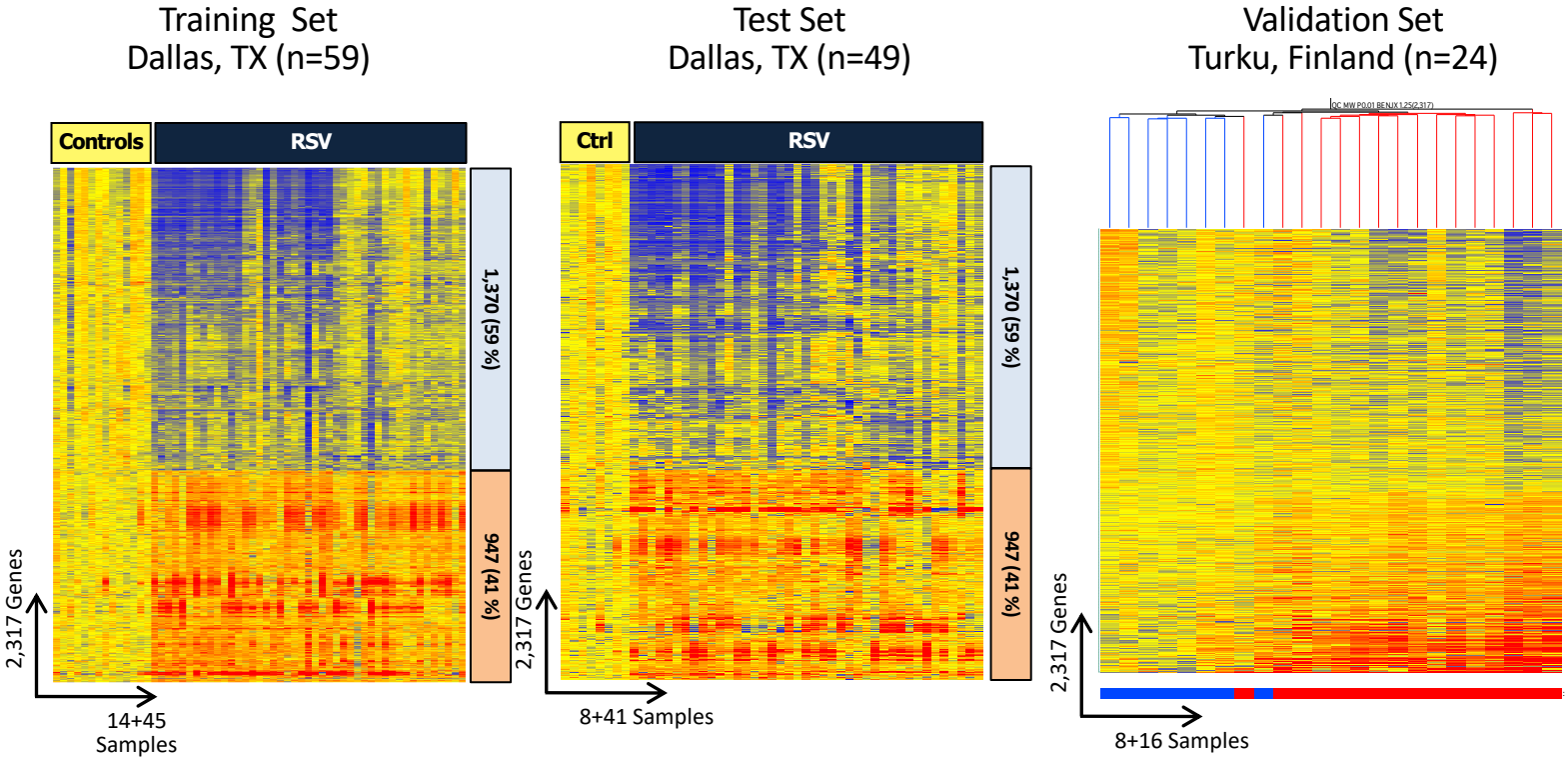
1. 1960’s: Formalin-inactivated vaccine associated with enhanced disease
2. Live attenuated vaccines: need to balance attenuation vs immunogenicity
3. Immune system immaturity and peak of severe disease
4. Lessons from studies on maternal antibodies



Hall et al Pediatrics 2013

Immune System Immaturity

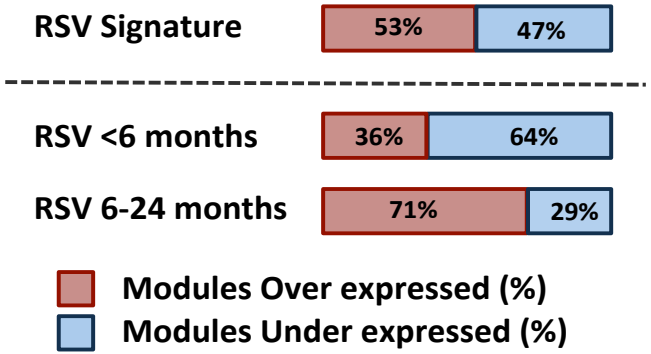
Transcriptional Profile in Children with RSV Bronchiolitis

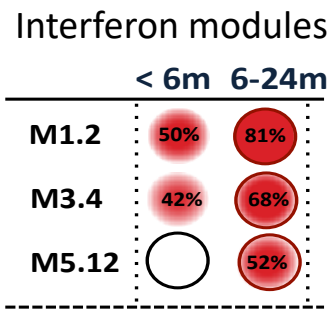


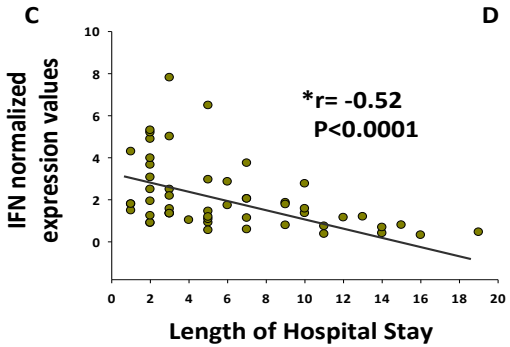
Mann-Whitney <0.01, Benjamini MTC x1.25 fold change

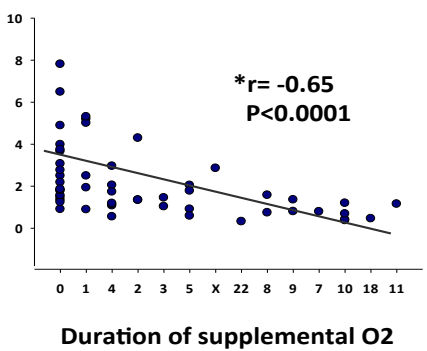
Mejias et al, PLOS Medicine 2013:10(11):e1001549

RSV-induced immune profiles by age group





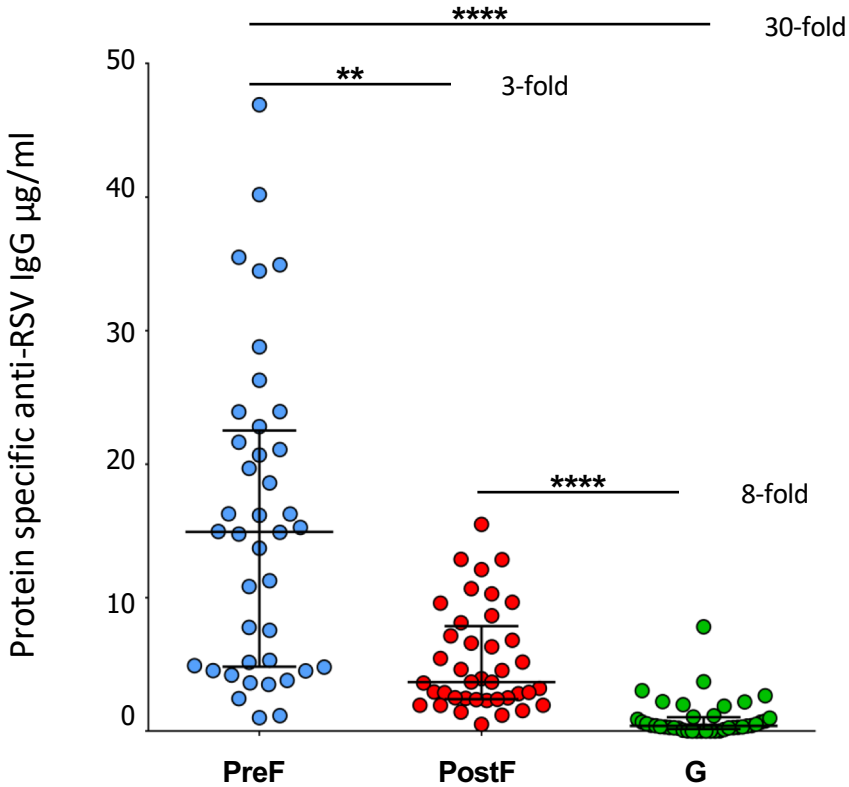




Mejias et al, PLOS Medicine 2013:10(11):e1001549

Understanding impact of maternal antibodies

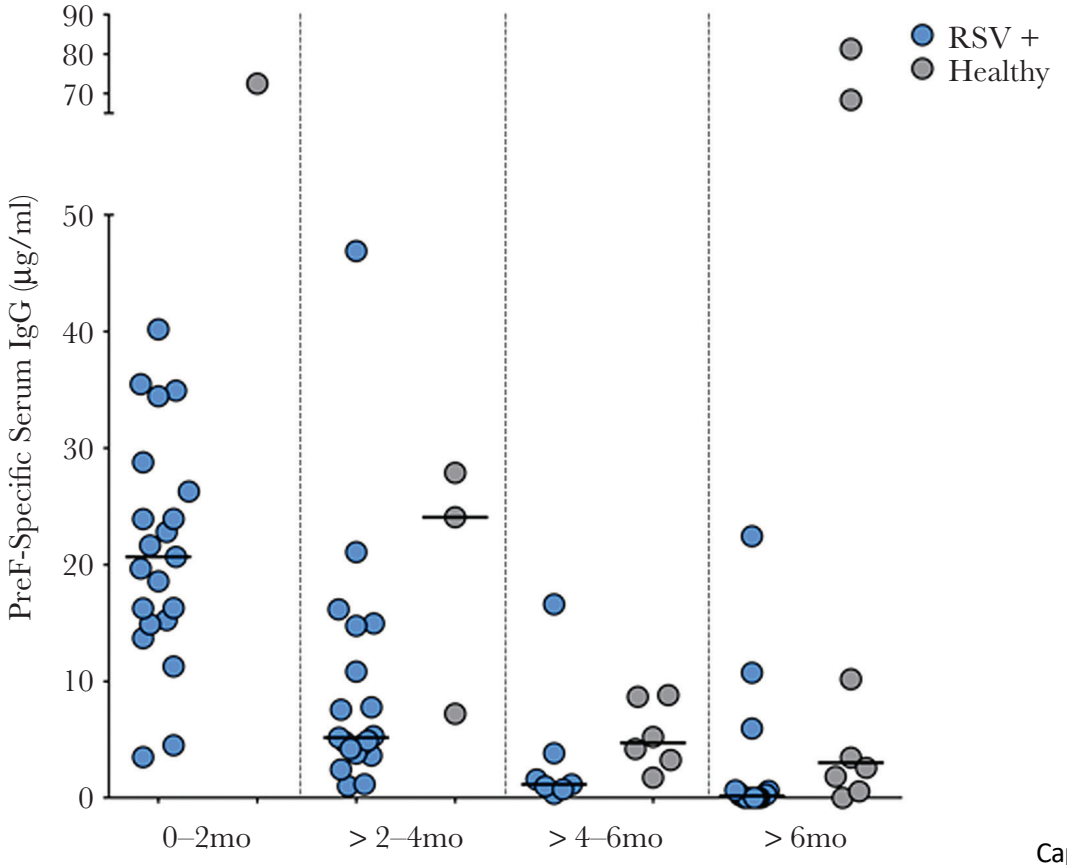
Serum IgG against PreF are the most abundant antibodies in infants



Capella C, et al; JID 2017

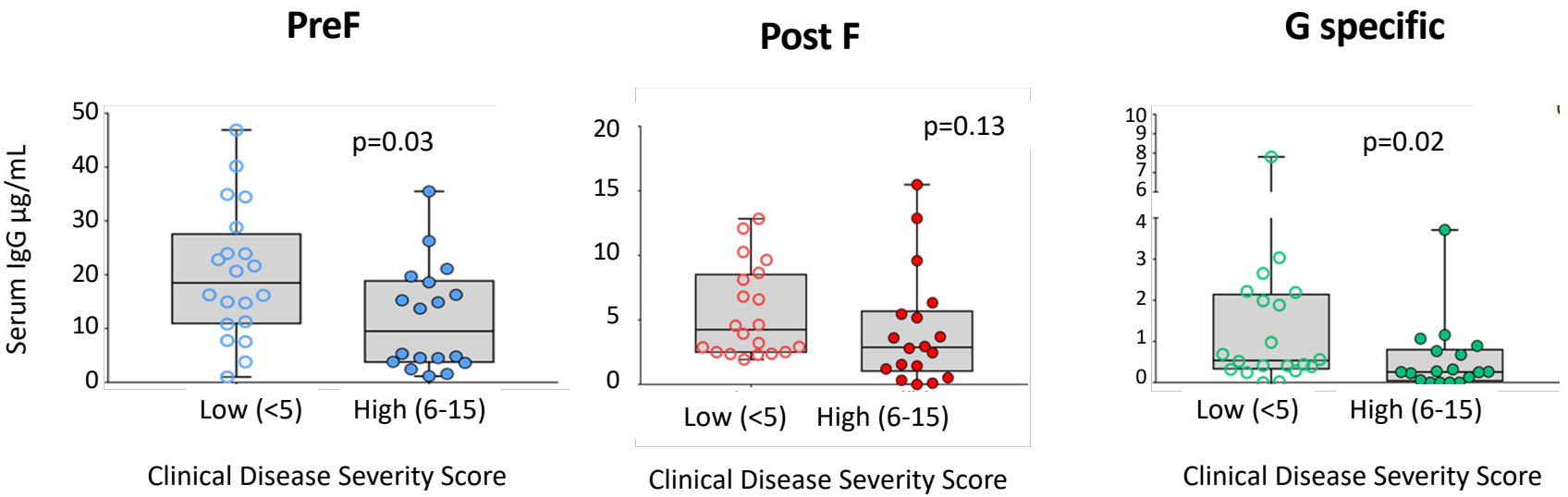
Patients ≤ 4 months of age
n = 44; 40 Acute patients (Circles).
Statistics: Kruskal-Wallis followed by Dunn's Test to adjust for multiple comparisons.

Serum PreF antibodies inversely correlate with age



Capella C, et al; JID 2017

RSV patients with lower severity scores had higher PreF- and G-specific IgG antibodies

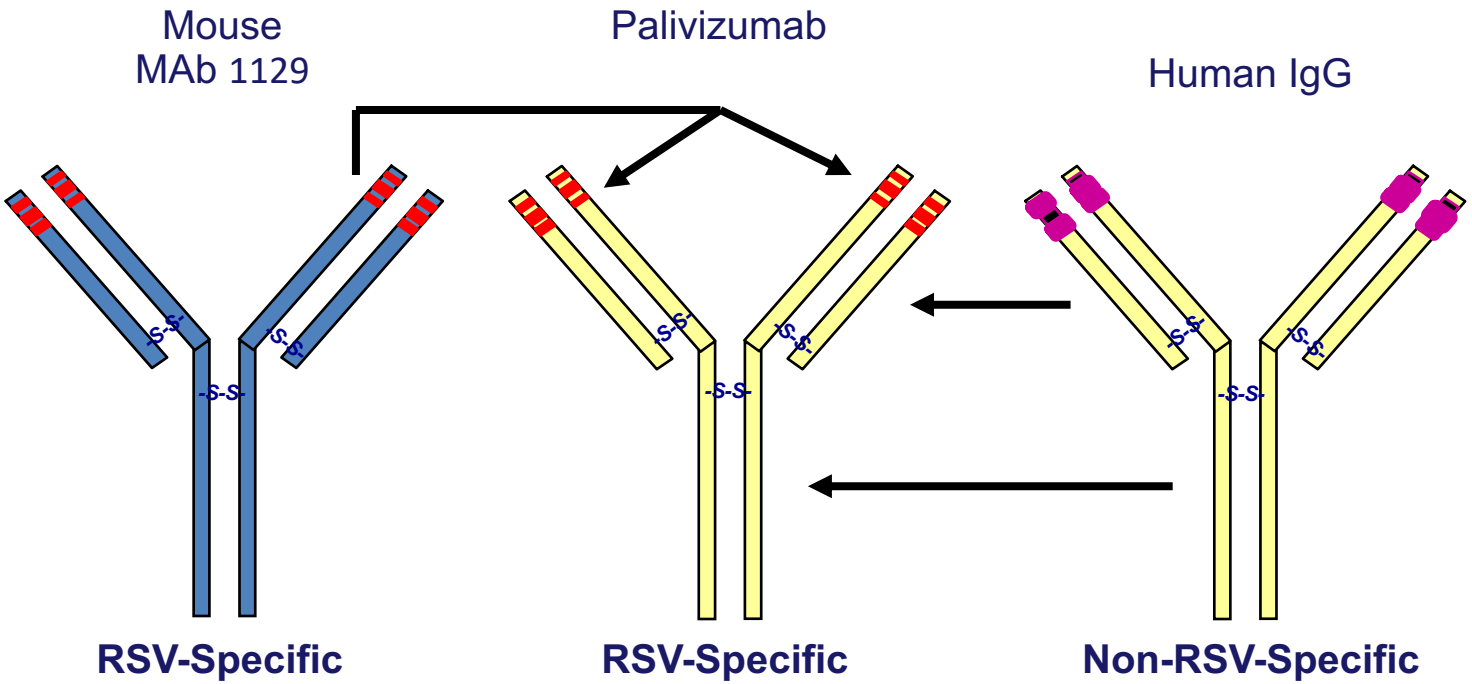


Patients ≤ 6 months of age
n = 38 hospitalized patients
Statistics: Mann-Whitney, median with (IQR).

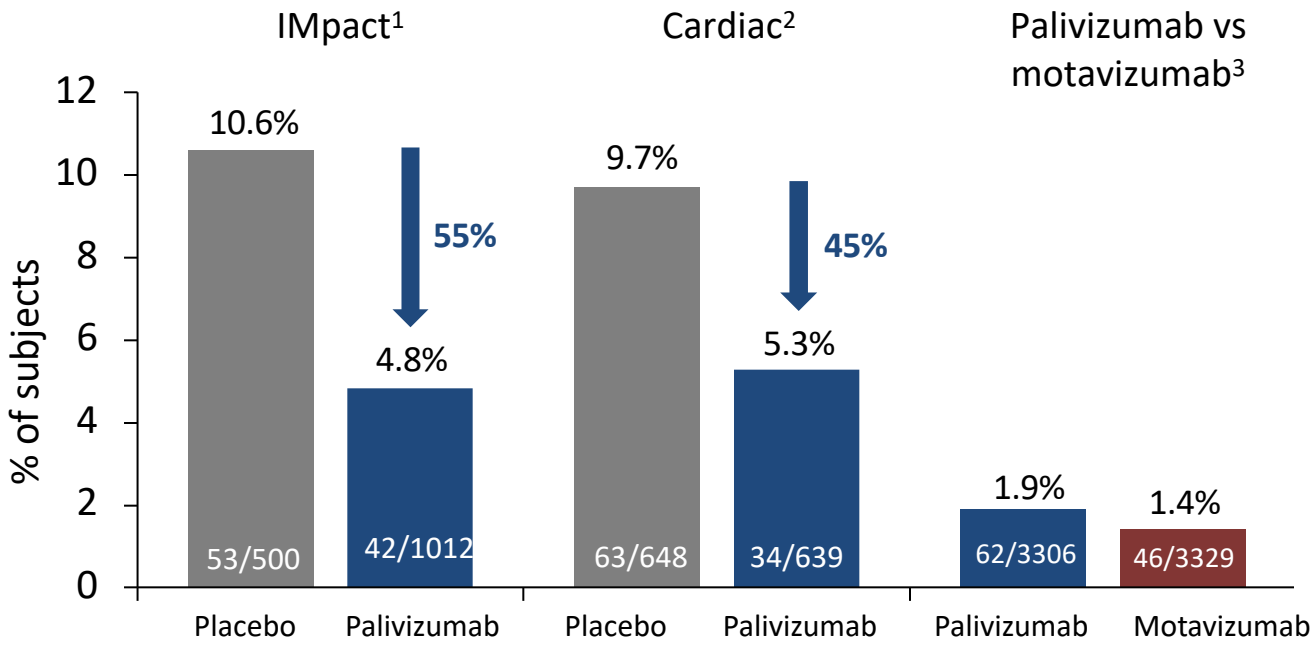
Capella C. et al. J Infect Dis 2017; 216 (11): 1398-1406

Anti-RSV mAbs as a preventive strategy: What is the evidence?

Construction of palivizumab: A humanized monoclonal antibody

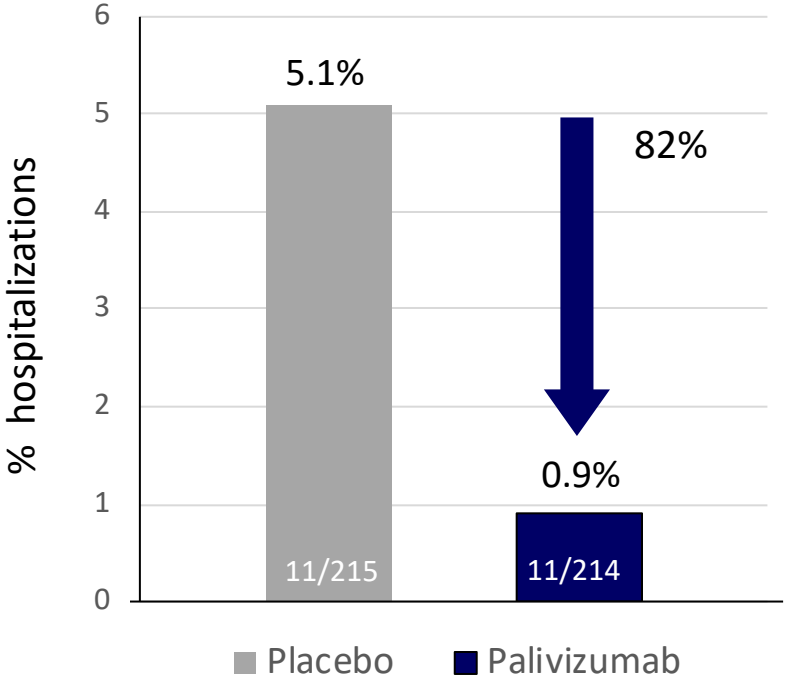


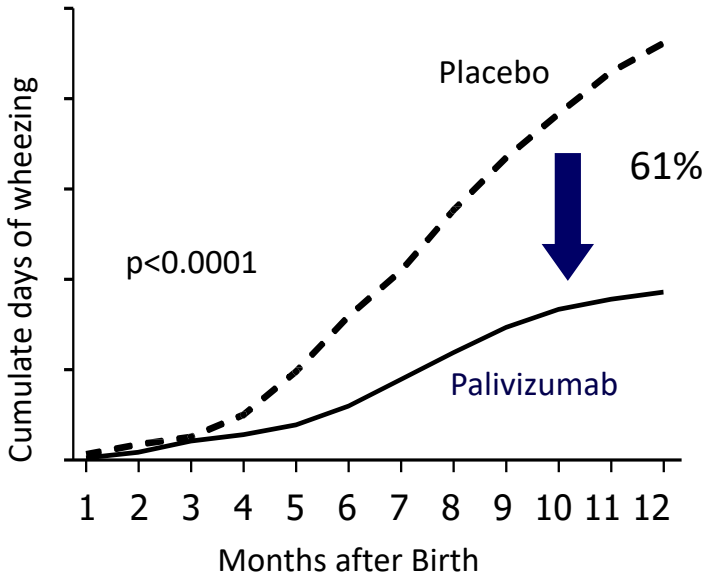
Randomized studies demonstrate efficacy of palivizumab in reducing RSV hospitalizations



1. The IMpact-RSV Study Group. Pediatrics 1998; 102:531–7;
2. Feltes TF, et al. J Pediatr 2003; 143:532–40;
3. Carbonell-Estrany X, et al. Pediatrics 2010; 125:e35–51

RSV prophylaxis reduces hospitalizations and recurrent wheezing in late preterm infants (MAKI)



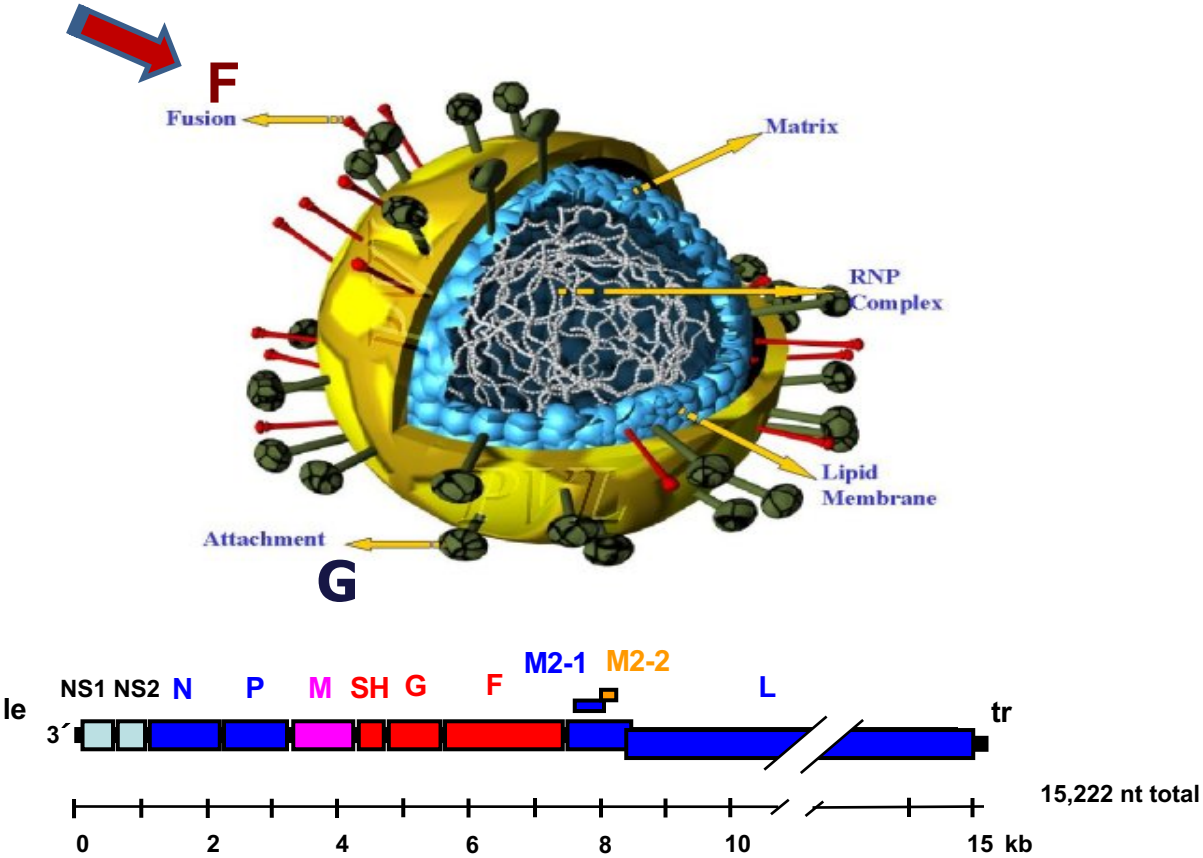


Blanken M, et al NEJM 2013; 368 (19): 1791-9

RSV F Protein: An Update

1. Conserved and excellent target for therapeutic interventions
2. Structures of both Pre- and Post-Fusion F have been resolved
3. Pre-Fusion F (PreF) contains the most potent neutralizing sites
4. PreF considered ideal target for vaccines and mAbs

RSV: The Virus



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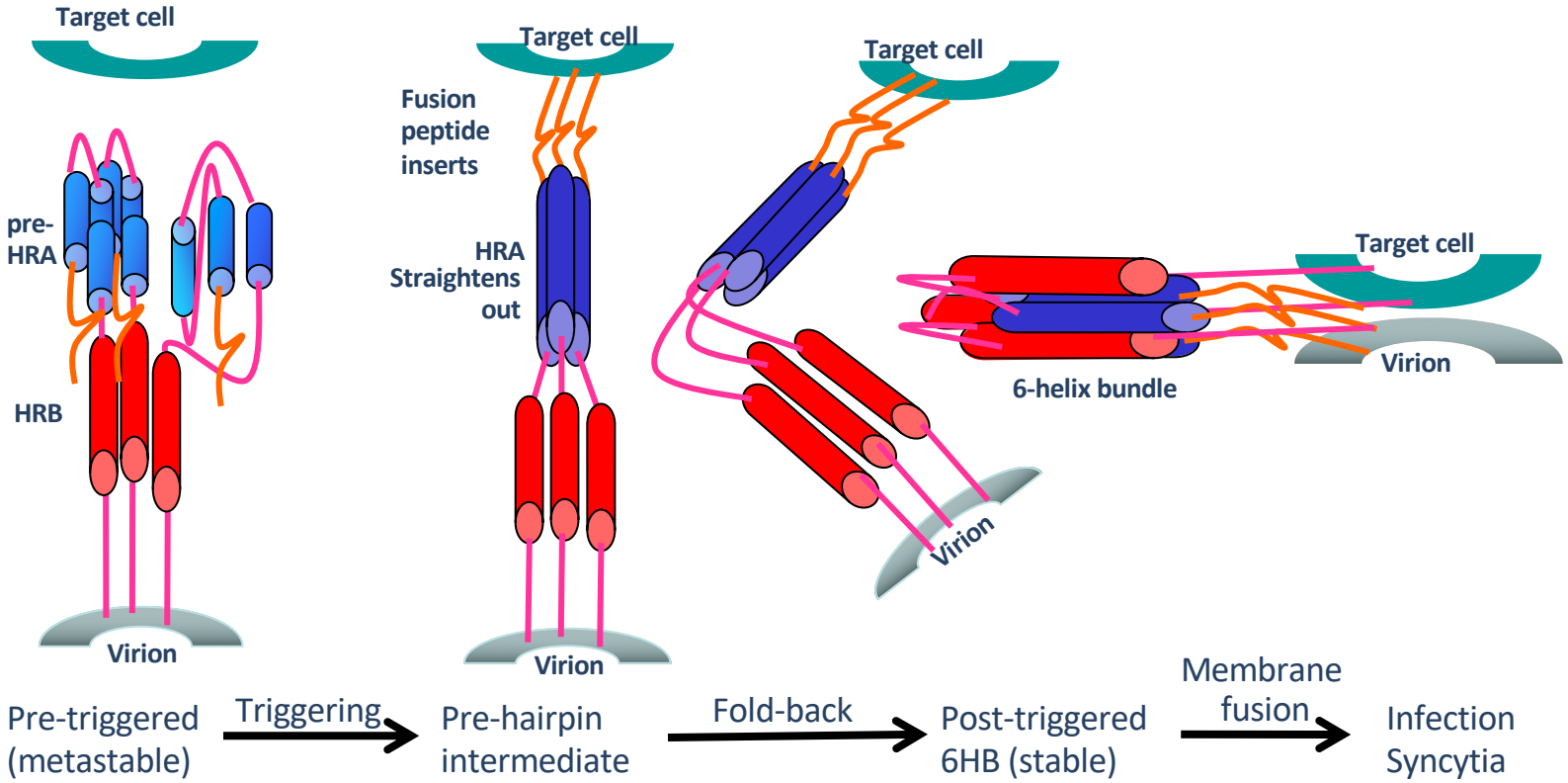
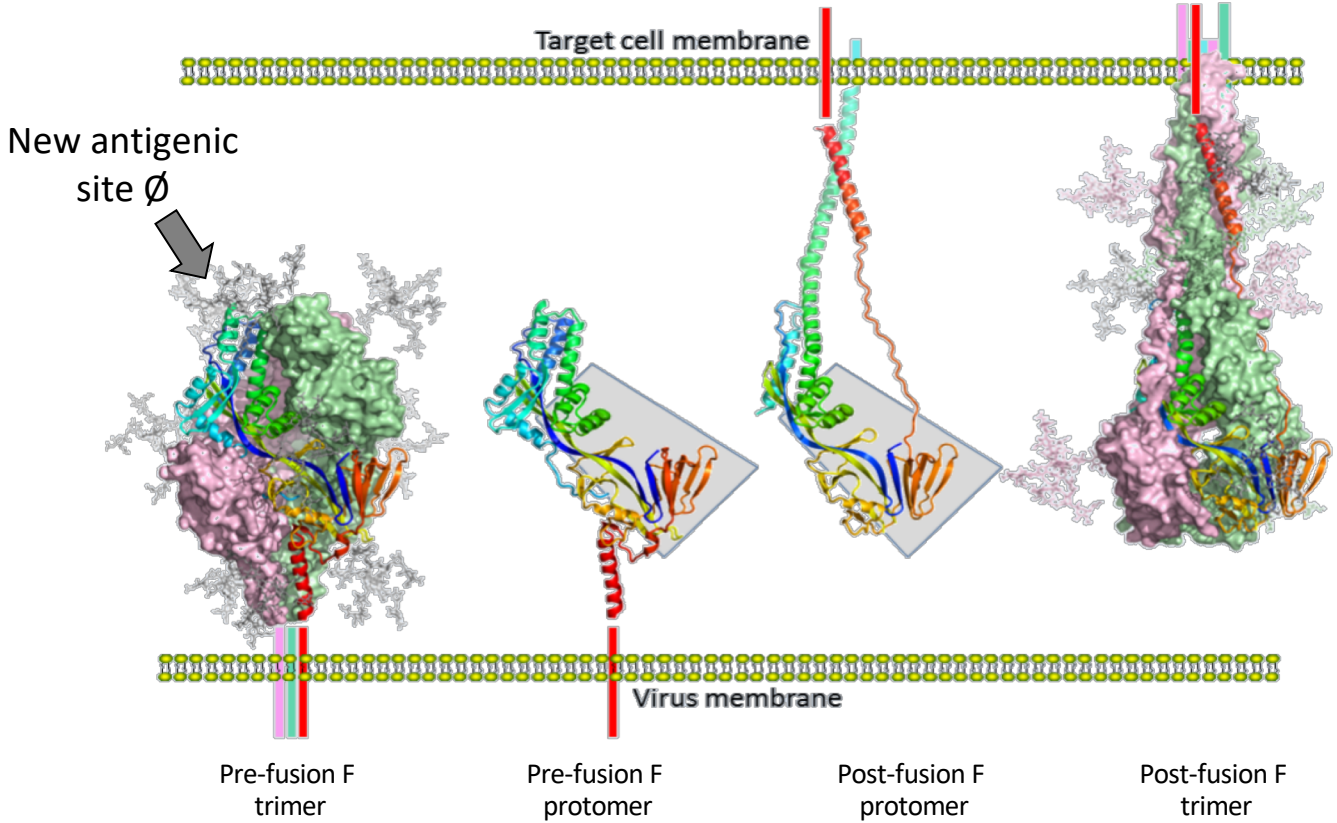
F protein trimer-mediated fusion



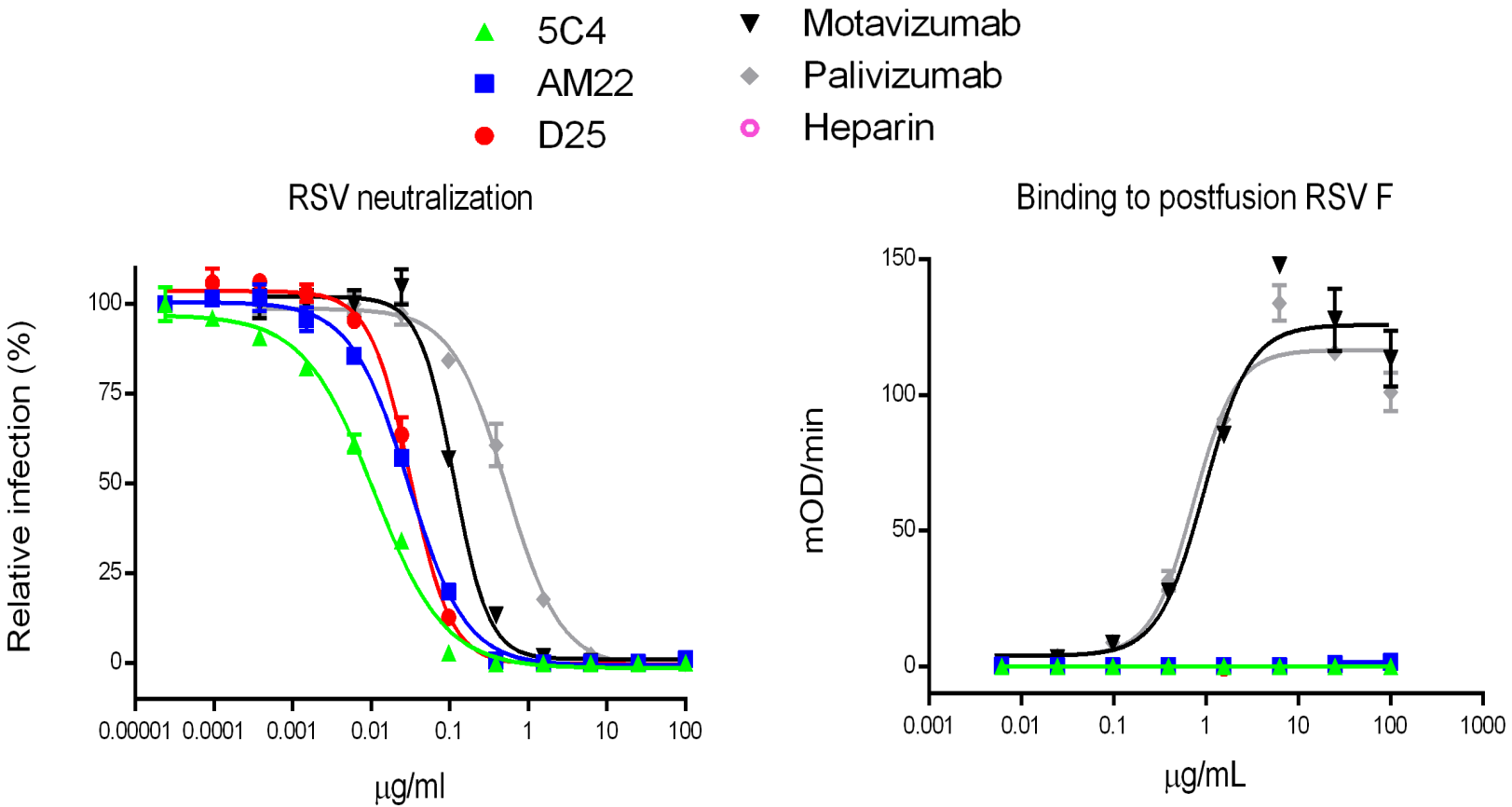
Modified from McLellan JS, Ray WC, Peeples ME. Curr Top Microbiol Immunol 2013; 372:83–104

RSV F protein: Pre-fusion vs Post-fusion

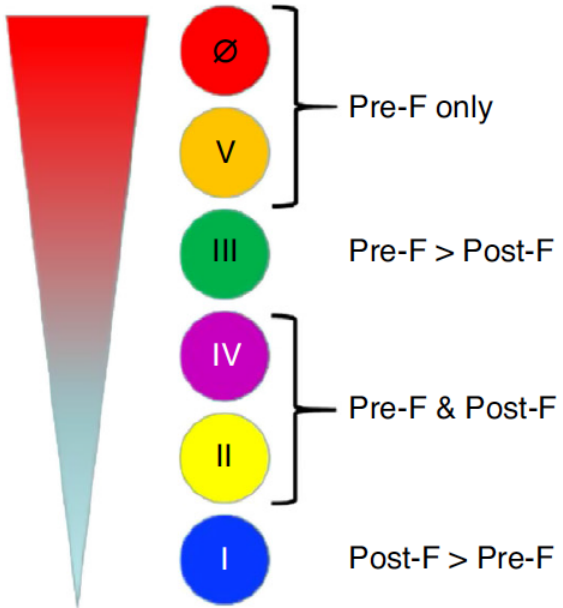


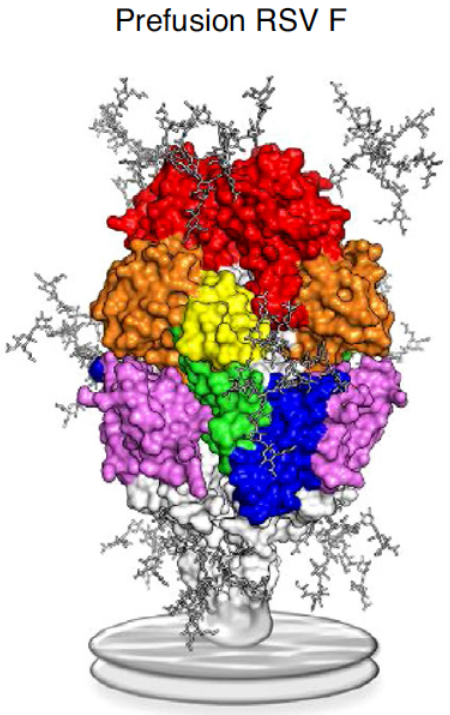
Modified from McLellan JS, et al. Science 2013; 340:1113–7

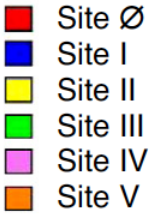
Potent neutralizing mAbs bind PreFusion F

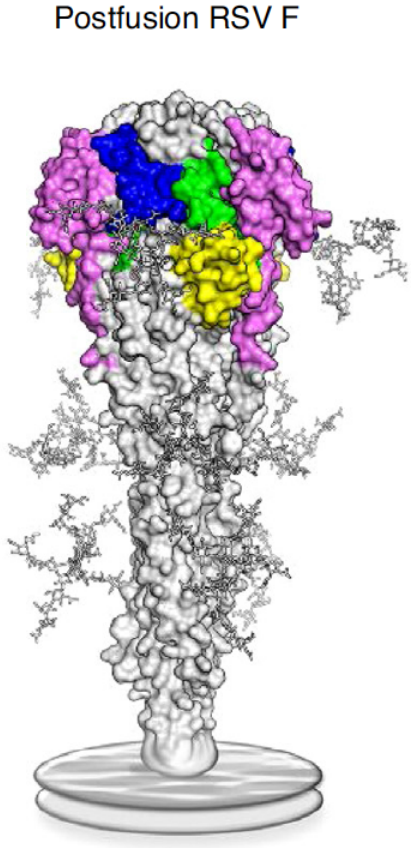


RSV PreF and PostF antigenic sites



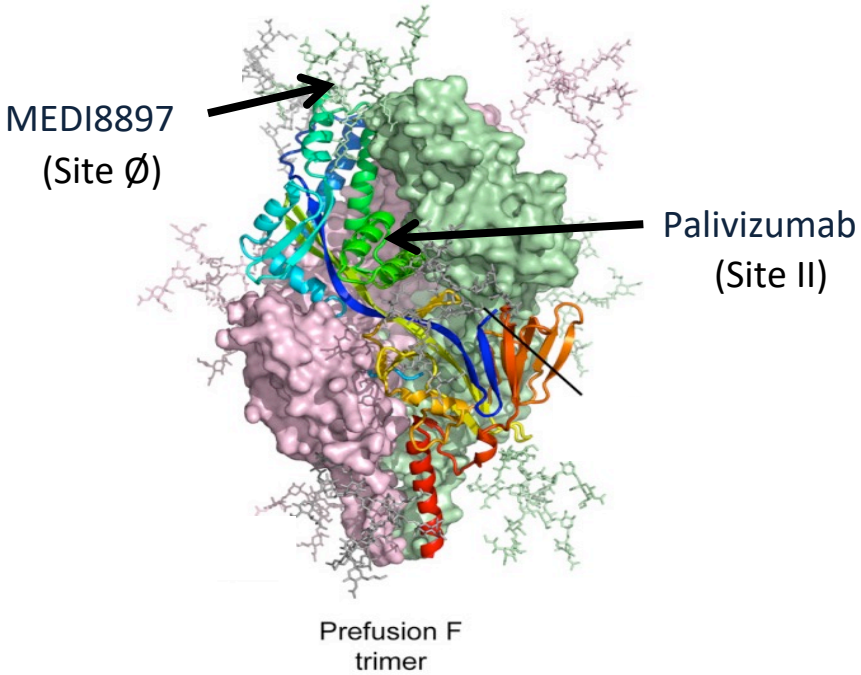






Graham B, Current Opinion in Virology 2017; 23:107

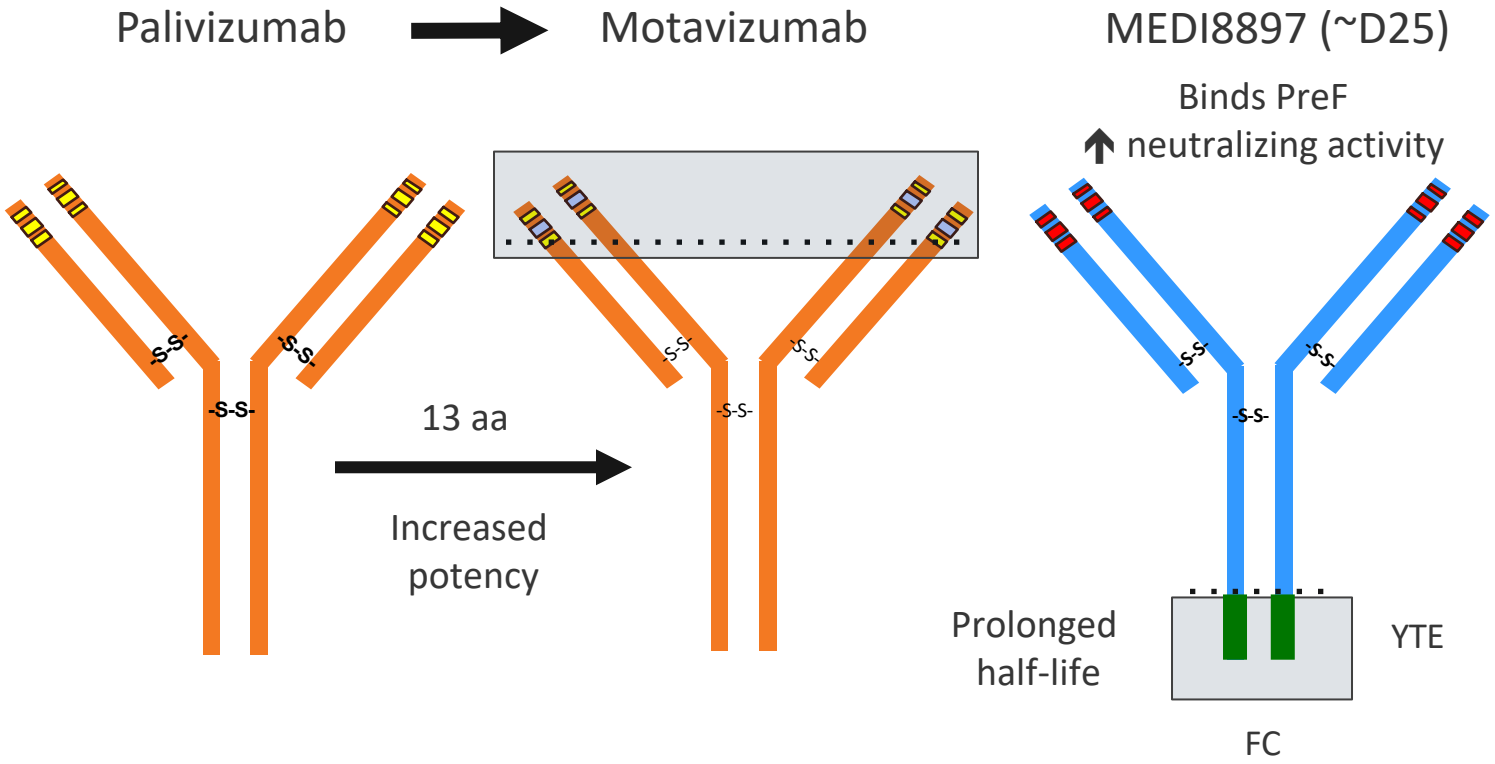
MEDI8897 blocks RSV F protein-mediated fusion



- Fully human IgG1 mAb derived from human B-cells
- Targets a unique antigenic site on pre-fusion RSV F (distinct from palivizumab)

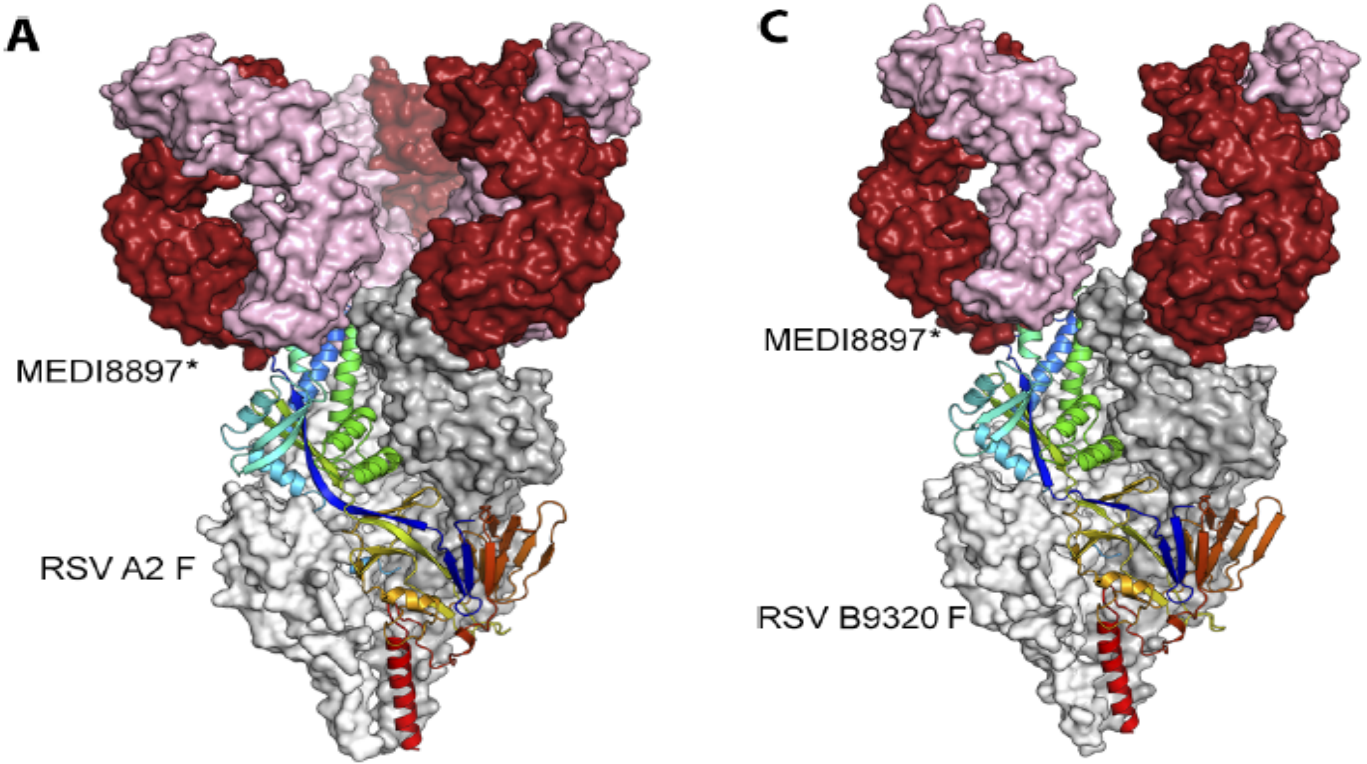
McLellan JS, et al. Science 2013; 340:1113–7; Synagis Summary of Product Characteristics, as approved in January 2016 (EMEA/H/C/000257-N/0110); Dubovsky F. 5th Asia Pacific Global Summit and Expo on Vaccines and Vaccination, 27–29 July 2015, Brisbane, Australia

Anti-RSV neutralizing mAbs



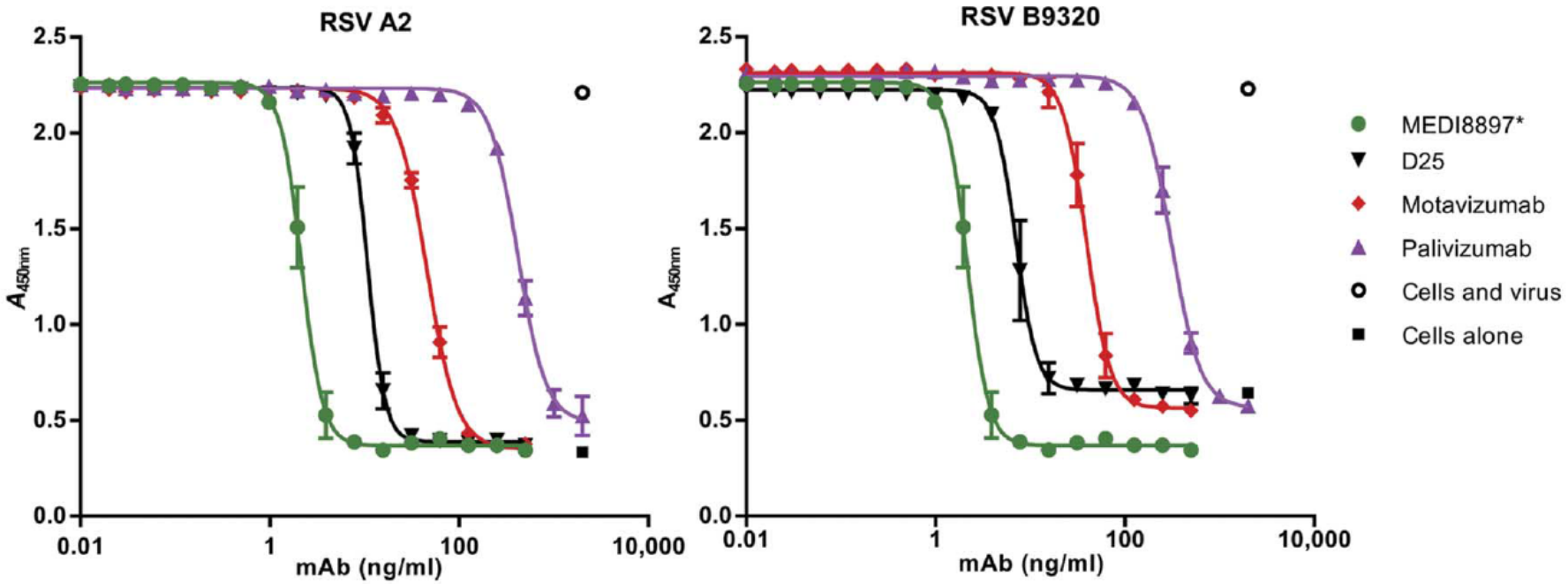
Wu H, et al. J Mol Biol 2007; 368:652–65; Wu H, et al. Curr Top Microbiol Immunol 2008; 317:103–23; McLellan JS, et al. Science 2013; 340:1113–7; Dubovsky F. 5th Asia Pacific Global Summit and Expo on Vaccines and Vaccination, 27–29 July 2015, Brisbane, Australia

Structure of PreF bound to new mAb



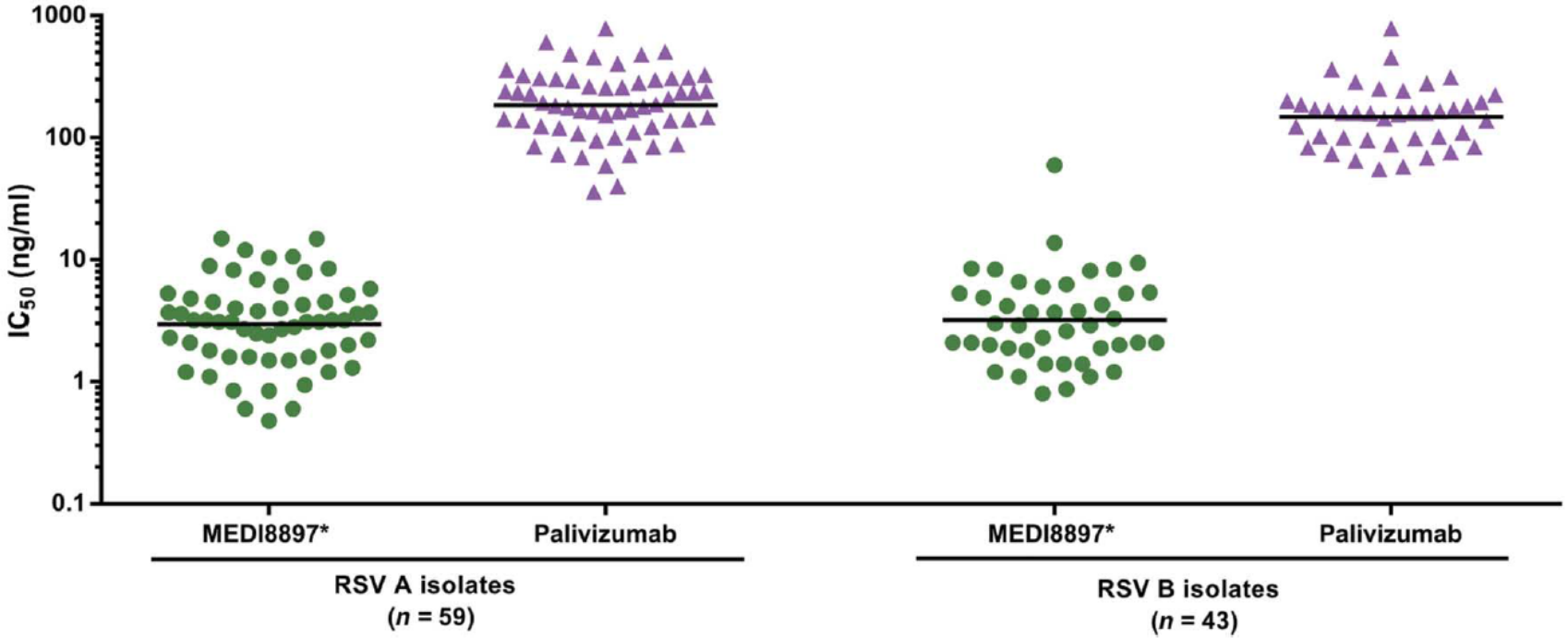
Zhu et al, Sci Transl Med 2017 eaaj1928

Comparative potency of new anti-RSV mAbs

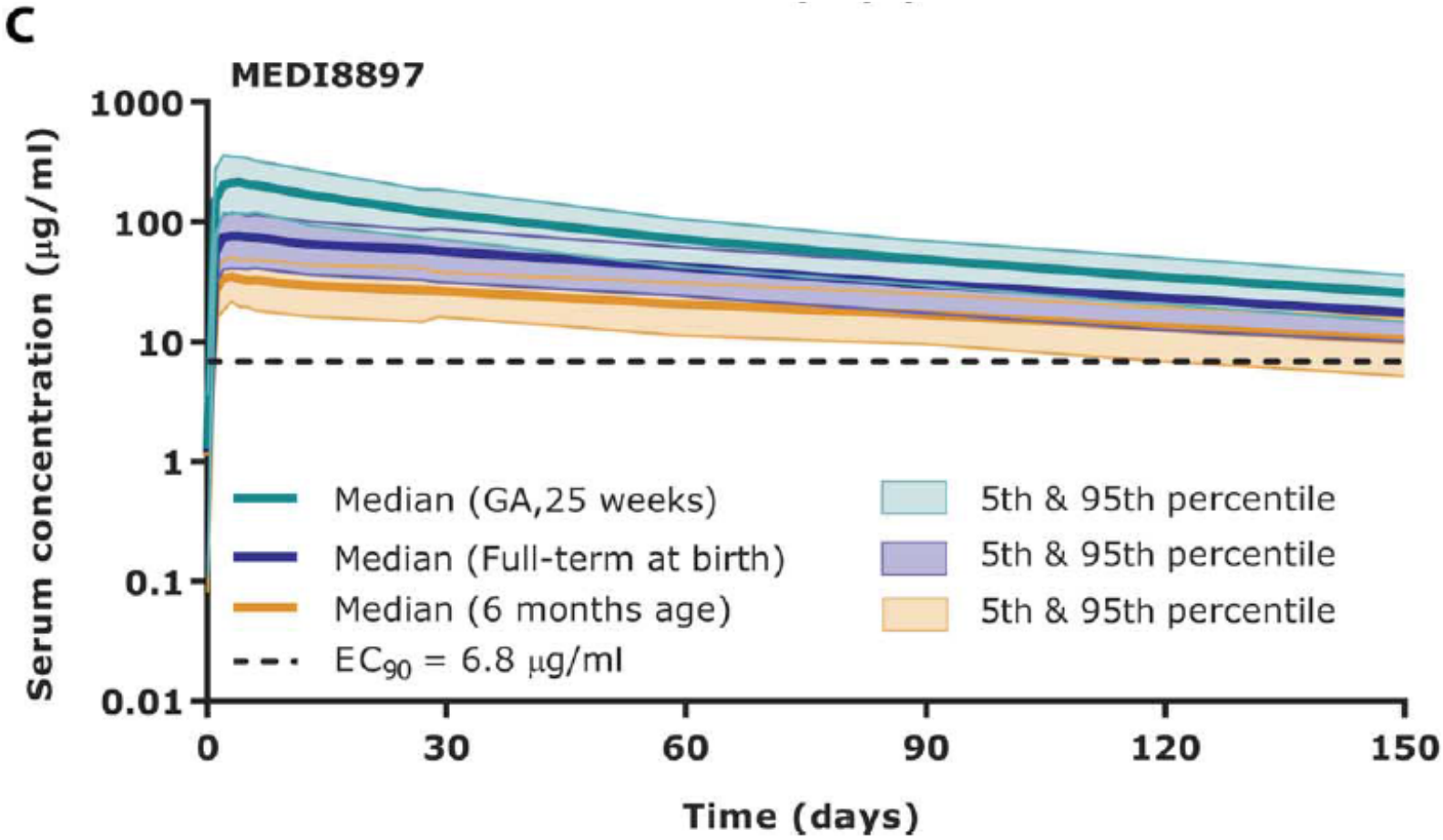


Zhu et al, Sci Transl Med 2017 eaaj1928

Comparative potency of MEDI8897 vs Palivizumab against a variety of clinical isolates

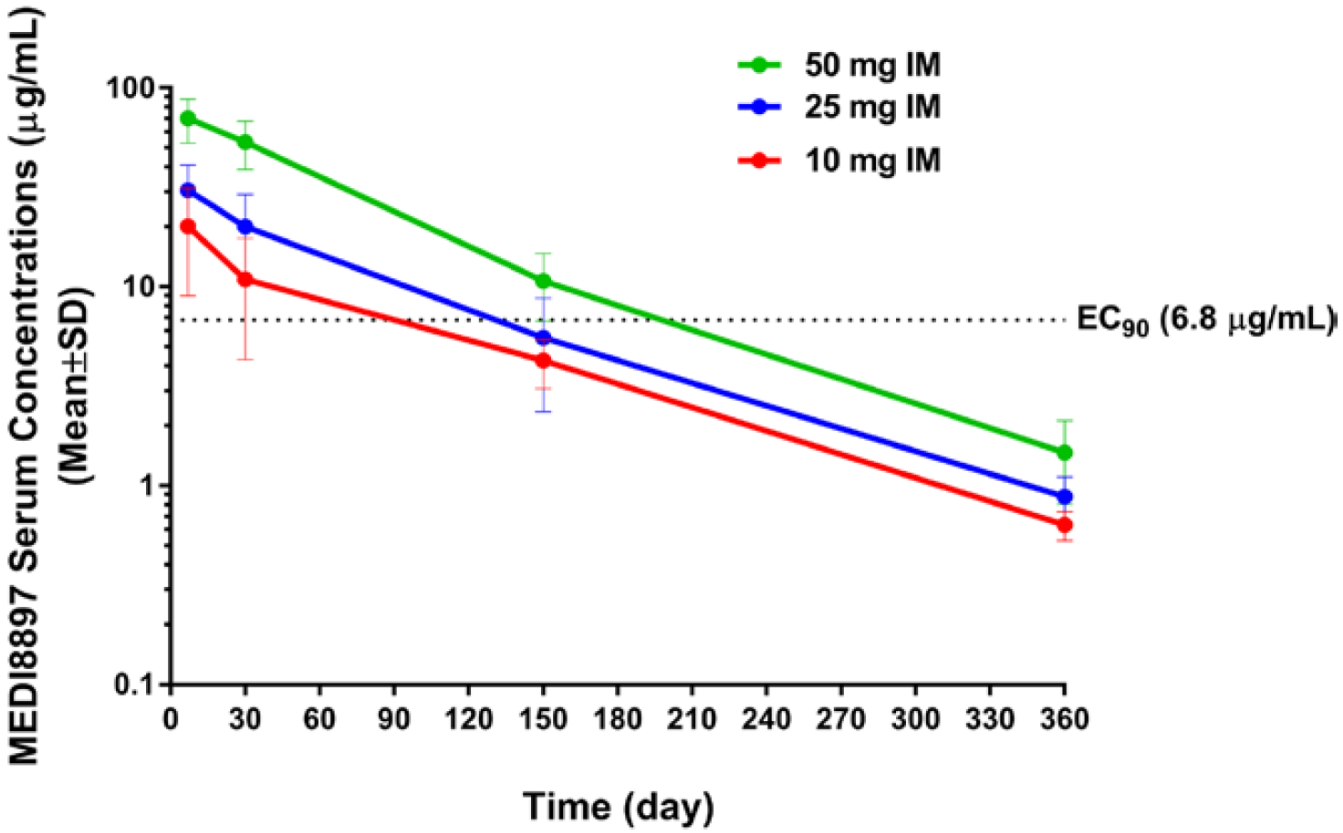


Zhu et al, Sci Transl Med 2017 eaaj1928



Zhu et al, Sci Transl Med 2017 eaaj1928

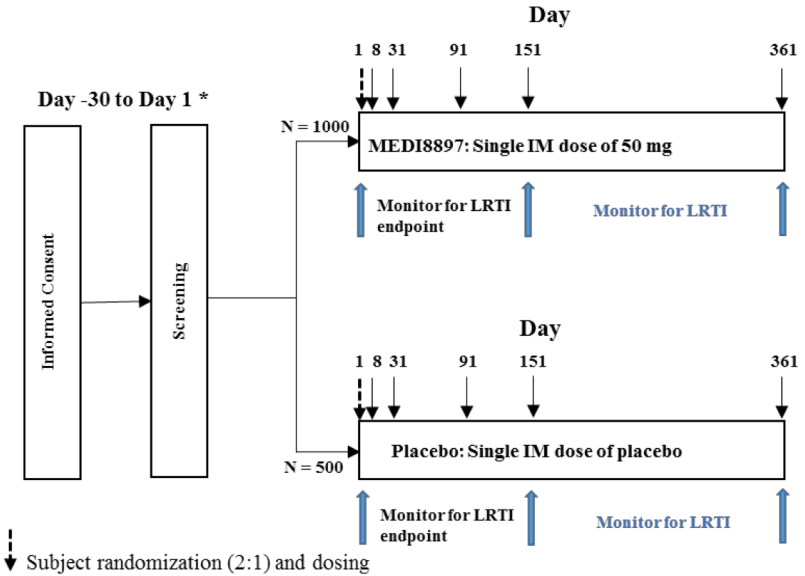
MEDI8897 serum concentrations time-profiles



Domachowske et al Pediatr Infect Dis J 2018;37:886

Phase 2b Study Design

Randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of MEDI8897 in healthy preterm infants



- PK and ADA samples collected during screening, on Day 91, 151 and 361 and at hospitalization for LRTI
- Safety assessments performed from screening through Day 361
- * Screening and Day 1 visits may occur on the same day

- **Study population**
  - **1453 preterm infants** 29 – 35 weeks gestational age (Synagis-ineligible per guidelines) **enrolled**
- **Primary endpoint**
  - Incidence of **medically attended LRTI** (inpatient and outpatient) caused by RT-PCR confirmed RSV for 150 days after dosing
- **Key secondary and exploratory endpoints**
  - Incidence of **hospitalizations** due to RT-PCR-confirmed RSV for 150 days after dosing
  - Safety, PK, and ADA
  - Assess healthcare utilization and caregiver burden

Courtesy of Dr. Pam Griffin

Case Definition for LRTI Endpoint

Villafana *et al*., Expert Review of Vaccines, 2017

Elements to evaluate for case definition of LRTI*

RSV	Physical Exam Findings	Medical Significance (Disease Severity Indicators)

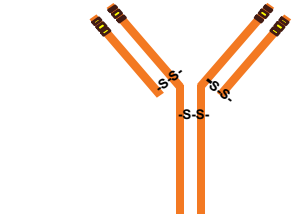
RSV confirmed:
 	
• Positive RT-PCR assay by central laboratory
	Documented findings localizing to lower respiratory tract:
	
	• Rhonchi
	• Rales
	• Crackles
	• Wheeze
		• Increased respiratory rate (bpm)
		  • ≥ 60 for < 2 mo
		  • ≥ 50 for 2-6 mo
		  • ≥ 40 for 6-24 mo
		• Hypoxemia
		  • O2 < 95% at ≤ 1800 meters
		  • O2 < 92% at > 1800 meters
		• New onset apnea
		• Nasal flaring
		• Retractions
		• Grunting
		• Acute hypoxic or ventilatory failure
		• Dehydration due to respiratory distress requiring IV hydration

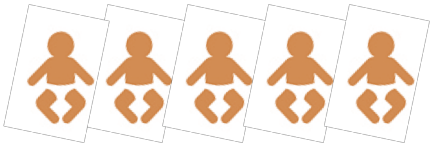
*To meet the case definition there must be at least one criterion from each column

Courtesy of Dr. Pam Griffin

Reinventing the role of mAbs for prevention of RSV

Palivizumab





MEDI8897